Neuropeptide Y Modulates L-Type Ca\(^{2+}\) Current During Heart Development

Alan E.G. Lomax, Keith A. Sharkey, Wayne R. Giles

A n interesting and potentially very important study\(^1\) in this issue of *Circulation Research* reports that during development of the mammalian heart, neuropeptide Y can significantly increase L-type Ca\(^{2+}\) current, thereby enhancing heart rate and strength of contraction. In this study, a combination of targeted deletion of the NPY gene, electrophysiological recordings, and immunoblot analysis of Ca\(^{2+}\) channel α\(_{1c}\) expression is used in an experimental design that involves study of hearts from pre- and postnatal animals at predetermined stages.\(^1\) These findings can perhaps be put in context by the following brief review of NPY physiology and pharmacology in mammalian tissue.

Neuropeptide Y (NPY) was identified by Tatemo and Mutt in 1982 through use of a novel chemical assay that detected the amidated C-terminal tyrosine residue of this 36-amino acid peptide.\(^2,3\) Isolated first from brain, it was soon discovered to be widely distributed throughout the body, primarily in postganglionic sympathetic nerves and often colocalized with norepinephrine.\(^4\) Indeed, NPY is the most widely distributed and abundant neuropeptide in the nervous system. NPY shares structural and functional homology with two other 36-amino acid peptides, pancreatic polypeptide (PP) and peptide YY (PYY).\(^4\) All three have a characteristic U-shaped tertiary structure termed the PP-fold.\(^5\) Four G protein–coupled receptors for the PP-fold peptides have been detected: these are the Y\(_1\), Y\(_2\), Y\(_3\), and Y\(_4\) receptors. The Y\(_1\) receptor has not been cloned, although a y\(_1\) receptor has been identified by molecular methods. It is designated with a lowercase “y\(_1\)” as, at present, it appears not to be functional.\(^5\) PP and PYY are primarily localized in endocrine and enteroendocrine cells of the pancreas and gastrointestinal tract, respectively.\(^4\)

The well-established physiological actions of NPY and the other members of this family are extensive and include stimulation of food intake,\(^6\) inhibition of anxiety,\(^7\) and control of seizures\(^8\) in the CNS, presynaptic inhibition of neurotransmitter release in the CNS and periphery,\(^4,8\) and vasoconstriction,\(^9,10\) inhibition of insulin release,\(^6\) and regulation of gastrointestinal secretions.\(^11\) and other actions in the periphery. In most cells studied, the effects of NPY are mediated by the four receptors mentioned above linked to pertussis toxin–sensitive G proteins of the G\(_4\) and G\(_o\) family.\(^5\) While inhibition of adenyl cyclase is a feature of the heterologous expression of the cloned receptors in cell systems, it does not fully explain the range of responses seen after stimulation of NPY receptors in tissues.\(^5,5\) It has been suggested that a pertussis toxin–insensitive G\(_4\) protein may also mediate the effects of Y-receptor stimulation. An interesting feature of NPY signaling is that NPY in its native form is a potent ligand for the Y\(_1\) receptor. A tissue-bound peptidase, dipeptidyl peptidase IV (CD26), cleaves the N-terminus to produce NPY3-36, which is a potent endogenous ligand for the Y\(_3\) and Y\(_4\) receptors.\(^12\)

NPY is found in the heart in neurons of the intracardiac ganglia and in postganglionic sympathetic nerves that innervate cardiac blood vessels, the intracardiac ganglia, endocardium, and myocardium.\(^13–15\) Fibers containing NPY innervate intrinsic parasympathetic cardiac neurons. During development in the rat, there is a gradual increase in the density of the NPY-containing neural elements. This is first detected during gestation, increases through to the first 3 weeks of postnatal life, and then remains stable through adulthood.\(^16\)

NPY is contained in large dense-cored secretory vesicles and appears to be stored separately from norepinephrine.\(^17\) It appears that the release of NPY is frequency-dependent, with greater release at higher frequencies of stimulation. NPY released from sympathetic nerve terminals can have direct postjunctional effects on cardiovascular tissues or can serve as a presynaptic regulator of neurotransmitter release.\(^9,10,18–20\) Y\(_1\) and Y\(_2\) receptors appear to mediate most of the cardiovascular effects of NPY, although the Y\(_3\) receptor has been implicated in the actions of NPY in the heart.\(^4,21,24\) Presynaptic inhibition of neurotransmitter release, postsynaptic enhancement of I\(_{\text{Na}}\),\(^22\) and reduction of I\(_{\text{Ca}}\) in cardiomyocytes,\(^23\) and the developmental regulation of cardiac ion channels (which appears to require synergistic interactions with norepinephrine) are due to Y\(_3\)-receptor activation.\(^18–21\) The post-synaptic vasoconstrictor effect of NPY on coronary blood vessels relies predominantly on Y\(_1\)-receptor activation.\(^9\)

In addition to this well-defined neurotransmitter role, NPY can stimulate or modulate angiogenesis.\(^18,25,26,29\) Increasing plasma levels of NPY correlate with severity of left ventricular hypertrophy in vivo, and NPY levels are known to increase in congestive heart failure in rats and humans, whereas overall plasma peptide content decreases.\(^27,30\) It is likely that this increase in NPY concentration reflects an increased density of sympathetic nerve terminals, although it should be noted that NPY is also found in platelets, immune cells, and endothelial cells.\(^5,30\) NPY acts at Y\(_3\) and Y\(_4\)
receptors on adult cardiomyocytes to exert hypertrophic effects by increasing protein synthesis and/or inhibiting protein degradation. It has also been shown to be a potent mitogen for vascular smooth muscle cells and endothelial cells and can stimulate endothelial cell adhesion, migration, proliferation, and differentiation. It is thought that these angiogenic properties of NPY improve revascularization of ischemic tissue.

The new findings in this study by Protas et al draw attention to a fundamental role of NPY in mouse heart functional development and pinpoint the L-type $\text{Ca}^{2+}$ channel as the effector. Additional work, including single $\text{Ca}^{2+}$ channel recordings, will be necessary to define the underlying mechanism(s). Functional studies, for example, using the approach of Potter and colleagues, in their studies of autonomic neurotransmission (and specifically the action of NPY and galanin in the mouse heart), will be of interest.

References

Key Words: neuropeptide Y • development • $\text{Ca}^{2+}$ channel • innervation • ventricle
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